AD_____

Award Number: DAMD17-00-1-0422

TITLE: Adequacy of Chemotherapy Dose Intensity Among African-American Women with HER-2/neu-Positive Breast Cancer

PRINCIPAL INVESTIGATOR: Jennifer J. Griggs, M.D.

CONTRACTING ORGANIZATION: University of Rochester
Rochester, New York 14627

REPORT DATE: September 2003

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 2003	Annual (1 Sep 2002 - 31 Aug 2003)

4. TITLE AND SUBTITLE
Adequacy of Chemotherapy Dose Intensity Among African-American Women with HER-2/neu-Positive Breast Cancer

5. FUNDING NUMBERS
DAMD17-00-1-0422

6. AUTHOR(S)
Jennifer J. Griggs, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Rochester
Rochester, New York 14627

E-Mail: jennifer_griggs@urmc.rochester.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)
No Abstract Provided.

14. SUBJECT TERMS
Breast Cancer; Racial disparity; quality of care;

15. NUMBER OF PAGES
22

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Introduction

Although the risk of breast cancer in African-American women is lower than in Caucasian women, African-American women have higher breast cancer fatality and case-fatality rates(1). The disparity in breast cancer outcome is not accounted for solely by differences in stage at diagnosis or in the biologic behavior of the disease(2). Differences in the quality of chemotherapy received by African-American women may provide an additional explanation for the poorer outcome among African-American women. Retrospective analyses suggest the beneficial impact of adjuvant chemotherapy on disease-free and overall survival in women with breast cancer is diminished when full doses of therapy are not received (3;4). The current recommendation is that patients undergoing adjuvant chemotherapy for breast cancer receive at least 80 to 85 percent of the planned doses (5). This multicenter study focuses on the clinical impact of suboptimal dose/dose intensity in women with HER-2/*neu*-positive tumors, a subgroup in whom optimal chemotherapy may be particularly critical. We are investigating the potential of relative chemotherapy dose (the ratio of actual to predicted doses) and dose intensity (which incorporates time to completion of adjuvant chemotherapy) as measures of quality of care. This study involves review of treatment records of subjects who have received chemotherapy for breast cancer and identification of the HER-2/*neu* oncogene on archival tumor specimens. The primary measures of chemotherapy quality (relative dose and dose intensity) will be related to the subjects' clinical outcome. The ultimate goal of the project is to design interventions targeting those factors that lead to lower dose intense chemotherapy in an effort to eliminate disparities in the quality of care of women with breast cancer.

Research Progress

Three sites are participating in this study as outlined below. Our original proposal included a fourth site, the University of North Carolina at Chapel Hill, but that site was not able to participate due to administrative reasons.

Please note that the results described below reflect the results of work funded both by the Department of Defense and the Doris Duke Charitable Foundation (DDCF). The DDCF funded the initial work for this research program. Reporting the results of the work separately would not accurately reflect the status of the project.

Eligible subjects are women who were treated with adjuvant chemotherapy for stage I, II, or III breast cancer between 1985 and 2000. Our original plan was to enroll a total of 500 subjects at three sites between 1985 - 1995, but we had to change the date to achieve planned subject numbers.

As of the date of this report, we are slightly behind schedule according to the approved Statement of Work submitted with the original grant application. Relocation of the Principal Investigator at Singing River Health System, Dr. Raymond Wynn and extensive changes in the management of clinical research have continued to delay progress at this site as described below.

The progress made for each task in the Statement of Work is described below:

Task 1. Identify eligible subjects by HER-2/*neu* staining on primary tumor samples and begin preparation for data collection, Months 1-12

a. Identify 500 eligible subjects at the three participating sites
b. Process and send samples for staining at central laboratory
c. Stain and interpret HER-2/*neu* staining in African-American subjects and Caucasian controls
d. Design database in preparation for data abstraction

Identification of Subjects
(Task 1a)

University of Rochester (Rochester, New York)
Using the Monroe County Tumor Registry and direct abstraction from chemotherapy (medical oncology) treatment records, we have identified 175 subjects treated for primary breast cancer at Strong Memorial Hospital between 1985 and 2000. Twenty-four are African-American, and 151 are non-Hispanic Caucasian. Fifteen of the 175 subjects are not eligible due to receipt of "sandwich radiation" (n = 8), primary systemic therapy (n = 4), and high-dose ("transplant") chemotherapy (n = 3). Demographic and treatment records have been retrieved and preliminary data collected and recorded on each eligible subject. Tumor blocks for all primary breast tumors have been located for all subjects (see Tasks 1b and 1c, below).

Henry Ford Health System (Detroit, Michigan)
Of 100 African-American and 100 Caucasian patients treated for primary breast cancer between 1990 and 1995 at the Henry Ford Health System, 200 are eligible and have complete information. (The dates of inclusion for eligible subjects are restricted by competition for tumor blocks within the Henry Ford Health System.) Review of the treatment records has been completed with quality checks for consistency and accuracy of the data. Tumor blocks for 85 subjects have been retrieved as of the date of this report (see Tasks 1b and 1c, below, for explanation of "missing" blocks).

Singing River Health System (Pascagoula, Mississippi)
Due to relocation of the Principal Investigator at this site (R. Wynn) to Singing River and major changes in the procedures required for approval of research studies, there had been delays in regulatory approval at this site. Approval by the Institutional Review Board at the Singing River Health System was delayed and only obtained in December 2001. Identification of subjects is complete, and data abstraction on 75 out of 132 potentially eligible subjects is complete. Although the Tumor Registry identified 132 subjects, 57 were ineligible for inclusion because of non-standard chemotherapy regimens (n = 12), primary chemotherapy (n = 6), no chemotherapy (n = 5), chemotherapy given elsewhere (n = 4), second breast primary (n = 3). Twenty-seven additional patients had records that could not be located.

Retrieval and Processing of Primary Breast Cancer Tumor Blocks
(Tasks 1b and 1c)

University of Rochester (Rochester, New York)
Tumor blocks of the primary breast tumors have been retrieved and processed for 66% of the deceased subjects (deceased n = 58, results on 39, blocks obtained and results pending on 10 more who have died in the past year). For subjects who are surviving but have recurrent disease (n = 28), most have had HER-2/*neu* staining performed on their primary tumors. This staining was performed (using the same methodology as for this study) solely for the purposes of appropriately treating their recurrent disease according to clinical practice and *not* for the purposes of this or any other research project. Appropriate quality control is in place at the University of Rochester for HER-2 staining. In addition, the vast majority were read/interpreted by the pathologist involved in this research project.

For the subjects who are surviving with no evidence of recurrent disease (n = 74), we have obtained informed consent from 38 subjects to perform HER-2 staining on archival tumor specimens and will be performing the staining in the next two weeks. Five subjects declined to have their archival specimens stained. We have yet to reach an additional 31subjects to obtain informed consent. We anticipate that we will have informed consent from the remaining subjects within the next month. As specified in the Annual Report for 2002, we had planned on having interpretation of the stained slides for overexpression of HER-2/*neu* by the middle of Year 3. We are planning on being done with the HER-2 staining and interpretation within the next 1 to 2 months.

Henry Ford Health System (Detroit, Michigan)
Of the 200 subjects at the Henry Ford Health System, we have HER-2 results on archival tumor in 49 subjects. Tumor blocks for 85 subjects have been retrieved as of the date of this report. Nineteen slides had no tumor on them, so HER-2 staining will not be possible on these samples. We have made multiple attempts to obtain actual tumor without success. We are confident that we have exhausted every possible avenue. We have 17 additional blocks awaiting re-staining or interpretation. Twenty-two of the subjects have missing tumor blocks.

Singing River Health System (Pascagoula, Mississippi)
As described above, the relocation of the Principal Investigator at this site (R. Wynn) to Singing River and major changes in the procedures required for approval of research studies led to delays in regulatory approval at this site. HER-2 staining is complete on 46 of the 60 subjects for whom we have tumor blocks available. Twelve tumor blocks have results pending. Three subject slides had no tumor on the slide. The remaining 15 subjects do not have tumors available at the treatment site.

Database Design
(Task 1d)

We have designed and refined a comprehensive database for data entry for subjects in this study using Access 97® (Microsoft Corporation). A copy of the worksheet version of this database

was attached as Appendix A for the annual report from Year 1. Data entry is being performed by the Study Coordinator at the University of Rochester.

Task 2. Abstraction of data from records of women whose tumors stain positive for overexpression of HER-2/*neu*, Months 13-24

a. Train data managers in data abstraction
b. Complete data abstraction from records of eligible subjects (approximately 40 subjects at each site = 160 total*)
c. Complete data entry and confirm consistency of data abstraction methods

*Original grant application specified 4 sites with 160 subjects with HER-2 positive tumors. As described in the first paragraph of the Research Progress, we now have three participating sites.

Train Data Managers in Data Abstraction
(Task 2a)

The data manager at Henry Ford Health System has been trained in the abstraction of data from the medical records with quality controls checks performed during the first 12 months of the study. The Principal Investigator and the Study Coordinator at the University of Rochester have been responsible for quality checks of the data. The Study Coordinator at Singing River Health System was been trained and has completed data collection. Quality checks were performed continuously on every record.

Data Abstraction from Records of Eligible Subjects
(Task 2b)

With funding from the Doris Duke Charitable Foundation and additional support, we have been able to complete data abstraction on all subjects who meet criteria—including subjects with both HER-2 positive and HER-2 negative tumors. The findings reported below are with all subjects. (Of note, the grant reviewers for this project advised inclusion of HER-2 positive and -negative subjects as well, but we needed additional support.)

University of Rochester (Rochester, New York)
We have completed medical record review for the 175 eligible subjects at this site. One hundred and sixty are eligible. Chemotherapy data are available on 100% of the 160 subjects. Some subjects were excluded for some analyses because of incomplete data.

Henry Ford Health System (Detroit, Michigan)
Complete data abstraction has been performed on 200 subjects.

Singing River Health System (Pascagoula, Mississippi)
As described above, approval of this protocol by the Institutional Review Board at the Singing River Health System was delayed only on December 14, 2001. Data abstraction is completed from 75 charts.

Data Entry and Confirm Consistency of the Data Abstraction
(Task 2c)

Data entry is complete except for the entry of the HER-2 results. There is continuous monitoring of the quality of data by the Principal Investigator and the Study Coordinator at the University of Rochester.

Task 3. Analysis of data, Months 25-36

a. Design multivariate regression models
b. Conduct analyses
c. Interpret data with investigators in Consortium
d. Begin designing interventions based upon results

We are currently in Month 37 of the project. We have not yet included the recently submitted information on the subjects in the Singing River Health System. We have demonstrated that African-American race and obesity independently predict for suboptimal chemotherapy (after controlling for age, coexisting medical problems, and socioeconomic status). We have also shown first cycle dose reductions (intentional dose reductions) are more common among these two groups of women and are less common among women of higher socioeconomic status. The methods and results, as well as our interpretation, are presented in detail in the Appendix, which is a recently-published manuscript. Again, the manuscript does not include the subjects who are to be included from the Singing River Health System.

The final portion of this project is the survival analysis in women whose tumors overexpressed HER-2. Our survival analysis will be complicated by the fact that there was a tremendous variation in the chemotherapy regimens used. We intend to calculate for each of the regimens the "summation dose intensity" as defined by Hryniuk and colleagues.(6) An additional limitation be the total number of subjects with HER-2 positive tumors. It is in these patients that dose proportion and relative dose intensity are most important.(7) The unanticipated number of missing blocks or tumors where the cancer could not be located has decreased the numbers substantially. We will repeat our published analyses with the subjects from the Singing River Health System and with the entire cohort of subjects (for all three sites).

Key Research Accomplishments

1. We have developed a network of breast cancer treatment sites.
2. We have demonstrated the feasibility of abstraction of specific chemotherapy treatment details at disparate treatment facilities.
3. We have developed a data collection system, comprehensive database, and statistical program to calculate dose and dose intensity of a variety of chemotherapy regimens for early-stage breast cancer.
4. We have demonstrated that disparities exist among different ethnic/racial groups in the administration of chemotherapy for early-stage breast cancer.
5. We have shown that obesity impacts chemotherapy prescribing patterns.

Reportable Outcomes

1. "Ethnicity and Age Predict Suboptimal Adjuvant Chemotherapy for Breast Cancer," Abstract and Podium Presentation, Annual Meeting of the Academy of Health Services Research, June 2001.
2. "Do Physician Prescribing Patterns Differ by Ethnicity in the Treatment of Localized Breast Cancer?" Abstract, Annual Meeting of the Academy of Health Services Research, June 2001.
3. "Racial Disparity in Breast Cancer Chemotherapy," Presentation at the Henry Ford Health System Cancer Center Grand Rounds, November 30, 2001.
4. "Racial Variation in Breast Cancer Adjuvant Therapy," Cancer Center Grand Rounds, Medical College of Virginia, Richmond, Virginia, February 2002.
5. "Quality of Breast Cancer Adjuvant Chemotherapy in African-American and Caucasian Women," Presented at the San Antonio Breast Cancer Symposium, San Antonio, Texas, December 2002.
6. "Disparities in Breast Cancer Treatment," Presentation, Rochester Clinical Research Curriculum, March 2003.
7. "Racial Disparities in Breast Cancer Care: Evidence for Systematic Disparities in Care" Grand Rounds, Roswell Park Cancer Institute, March 2003.
8. "Racial Disparity in the Dose and Dose Intensity of Breast Cancer Adjuvant Chemotherapy." Manuscript, *Breast Cancer Research and Treatment.* 81:21-31, 2003.

Conclusions

We have demonstrated that there is systematic disparity in the quality of adjuvant breast cancer chemotherapy according to race, obesity status, and income. Our results suggest that race/ethnicity predicts suboptimal chemotherapy for early stage breast cancer. Biological and socioeconomic differences do not explain the disparity in the treatment. Physician prescribing patterns appear to impart a significant impact on the outcome measures of our study, namely dose proportion and relative dose intensity. Women who are obese, African-American, and living below the median income are most likely to receive intentionally reduced chemotherapy doses. The systematic difference in the quality of chemotherapy may contribute to the higher case-fatality rate among African-American women and economically disadvantaged women with breast cancer.

Thus far, our measures are process measures of quality of care. If such dose reductions have an impact on outcome and the findings are generalizable to two other distinct geographic locales, we have developed a novel measure of quality of care. Interventions to eliminate the disparities in the quality of chemotherapy have the potential to improve the quality of care for minority women and economically disadvantaged women with breast cancer.

Management of localized breast cancer is complicated and requires coordination of care across multiple specialties. The project thus far has raised the possibility that the process of care differs between racial/ethnic and socioeconomic groups. We are applying for additional funding to expand this research program. Plans for ongoing work, in addition to that outlined in Task 3 including examining other patterns of care, such as (1) delays from diagnosis to surgery, (2) delays from surgery to the initiation of chemotherapy, (3) delays in the initiation or completion of adjuvant radiotherapy, (4) differences in side effects among different racial groups, and (6) differences in the use of supportive therapies such as granulocyte-colony stimulating factor.

With our ongoing program, we will also develop methods to investigate the reasons for disparities in the quality of adjuvant chemotherapy. It is our hypothesis that physicians prescribe intentional dose reductions (that is, first cycle dose reductions) because of perceived vulnerability of the patient. Our plans are to measure physician attitudes about their patients, including perceived social support. It is possible that physicians perceive their patients as having diminished social support and therefore prescribe reduced doses of chemotherapy. We will also be investigating management of symptoms of chemotherapy. The African-American women in our sample were more likely to discontinue chemotherapy before the planned number of treatments was administered. Communication difficulties regarding symptom management may lead to a patient terminating therapy before the standard number of treatments is completed. The ultimate goal is to design interventions to eliminate, or at least mitigate, such disparities. Developing the infrastructure for such interventions is a major goal of this research program.

Reference List

(1) Ries, L. A. G., Eisner, M. P., Kosary, C. L., Hankey, B. F., Miller, B. A., Clegg, L., and Edwards, B. K. SEER Cancer Statistics Review, 1973-1998. 2001. Bethesda, MD, National Cancer Institute.

(2) Eley JW, Hill HA, Chen VW, Austin DF, Wesley MN, Muss HB et al. Racial differences in survival from breast cancer. Results of the National Cancer Institute Black/White Cancer Survival Study. JAMA. 1994;272:947-54.

(3) Bonadonna G, Valagussa P. Dose-response effect of adjuvant chemotherapy in breast cancer. New Engl J Med. 1981;304:10-15.

(4) Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: The results of 20 years of follow-up. New Engl J Med. 1995;332:901-6.

(5) Goldhirsch A, Gelber RD. Understanding adjuvant chemotherapy for breast cancer. N Engl J Med. 1994;330:1308-9.

(6) Hryniuk W, Frei E, III, Wright FA. A single scale for comparing dose-intensity of all chemotherapy regimens in breast cancer: summation dose-intensity. J Clin Oncol. 1998;16:3137-47.

(7) Muss HB, Thor AD, Berry DA, Kute T, Liu ET, Koerner F et al. c-*erb*B-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. New Engl J Med. 1994;330:1260-1266.

Breast Cancer Research and Treatment **81:** 21–31, 2003.

Report

Racial disparity in the dose and dose intensity of breast cancer adjuvant chemotherapy

Jennifer J. Griggs[1,2], Melony E.S. Sorbero[3], Azadeh T. Stark[4], Susanne E. Heininger[1], and Andrew W. Dick[2]

[1]*Department of Medicine, Hematology/Oncology;* [2]*Department of Community and Preventive Medicine University of Rochester, Rochester, NY;* [3]*RAND, Pittsburgh, PA;* [4]*Henry Ford Health System, Josephine Ford Cancer Center, Detroit, MI, USA*

Key words: breast cancer, chemotherapy, obesity, racial disparity

Summary

Purpose. The purpose of this study was to investigate the impact of race and obesity on dose and dose intensity of adjuvant chemotherapy.

Methods. We abstracted data on patient/tumor characteristics, treatment course, physicians' intention to give a first cycle dose reduction, and reasons for dose reductions/delays from oncology records of 489 women treated from 1985 to 1997 in 10 treatment sites in two geographical regions. Administered doses and dose intensity were compared to standard regimens. Multivariate regression models determined the impact of race and body mass index (BMI) on dose proportion (actual:expected doses) and relative dose intensity (RDI) controlling for patient characteristics, comorbidity, chemotherapy regimen, site, and year of treatment. Logistic regressions explored race and BMI versus use of first cycle dose reductions.

Results. African-Americans received lower chemotherapy dose proportion and RDI than whites (0.80 vs. 0.85, $p = 0.03$ and 0.76 vs. 0.80, $p = 0.01$). In multivariate analyses, dose proportion was 0.09 lower ($p = 0.002$), and RDI was 0.10 ($p < 0.001$) lower in non-overweight African-Americans than whites. Obesity was associated with lower dose proportion ($p < 0.01$) and RDI ($p < 0.03$). Race and BMI were independently associated with first cycle dose reductions. Non-overweight African-Americans ($p < 0.05$) and overweight and obese African-American and white women ($p < 0.001$) were more likely to have first cycle dose reductions than non-overweight whites.

Conclusion. We identified systematic differences in the administration of chemotherapy given to African-Americans and to overweight and obese women. These differences may contribute to documented disparities in outcome.

Introduction

The incidence of breast cancer is lower in African-American women, but breast cancer mortality rates and case fatality rates among African-Americans are consistently higher than among whites [1]. The incidence of breast cancer in 1999, for example, was 123.9 per 100,000 in black women versus 143 per 100,000 in white women, but corresponding mortality rates were 35.8 per 100,000 in blacks versus 26.3 per 100,000 in whites [1]. Even after correction for stage at presentation and tumor biology, disparities in outcome persist [2–4]. Adjustment for socioeconomic status (SES) accounts for some but generally not all of the association between race and poorer outcome [2, 3, 5–10].

African-Americans treated on chemotherapy protocols appear to benefit from adjuvant chemotherapy with not only the same relative risk reduction in breast cancer mortality but also similar stage-specific outcome [11, 12]. This finding supports the conjecture that uniform treatment results in uniform outcome and argues against the hypothesis that race confers an independent deleterious effect on disease-specific outcome.

Large retrospective analyses suggest that the beneficial impact of adjuvant chemotherapy on disease-free and overall survival in women with breast cancer is diminished when full doses of therapy are not given [13–17]. Studies addressing the use or planned use of adjuvant therapy in African-Americans and whites have generally not demonstrated disparities in the use or intention to use chemotherapy [3, 18].

We hypothesized that, among women who do receive chemotherapy, there are systematic differences in the administration of chemotherapy given to African-American and white women. The possibility that differences exist in the delivery of chemotherapy has been raised [2, 19] but not well studied. We also investigated the impact of obesity on prescribing patterns for African-American and white women undergoing adjuvant breast cancer chemotherapy. The practice of dose reduction in overweight and obese women continues [20] despite evidence that using actual body weight for chemotherapy dose calculations is safe [21, 22]. As obesity is more prevalent in African-Americans [23, 24], the practice of basing doses on ideal or adjusted body weight might lead to systematically lower doses in African-Americans.

Subjects and methods

Study subjects. We identified African-American and white women as potentially eligible using the Monroe County (New York) and Henry Ford Health System (Michigan) tumor registries. Subjects identified were treated at 10 treatment sites, including university and community hospitals (five of six treatment sites in Rochester, New York and all five medical oncology treatment sites within the Henry Ford Health System in Detroit, Michigan). Eligibility criteria included treatment between 1985 and 1997 with cyclophosphamide-containing adjuvant chemotherapy for localized or regional (stages I, II, or III) breast cancer. Patients treated with primary (neoadjuvant) chemotherapy, chemotherapy interrupted by radiation ('sandwich radiation'), or on high-dose chemotherapy protocols were excluded. We also excluded women who had had a previous breast cancer.

Data collection. The University of Rochester Research Subjects Review Board (RSRB #08217) and the Henry Ford Health System Institutional Review Board (HFHS IRB #900) approved the data collection protocol. Six trained abstractors performed the chart audits. A senior health project nurse at the University of Rochester repeated the data abstraction on at least 30 charts reviewed by each of the six abstractors and on a random sample of 125 subjects included in the final database. The senior project nurse did all of the data entry.

We abstracted detailed information from the medical oncology charts and treatment records on (1) subject characteristics, including age, self-assigned race/ethnicity, insurance type, address for census block group assignment, height, weight, and coexisting medical conditions (see below), (2) tumor characteristics, including tumor size, number of lymph nodes involved, estrogen receptor (ER) and progesterone receptor (PR) status, and histologic grade, (3) chemotherapy regimen and treatment course, dates of treatment, dose of each drug administered, body surface area used for calculation of the drug doses, and whether a dose reduction from standard doses was used for the initial cycle of chemotherapy, (4) treatment site, (5) reasons for changes in chemotherapy doses or delays in treatment, side effects, hospitalizations, and discontinuation of therapy. White blood cell counts and absolute neutrophil counts (ANC) were recorded whenever available. Coexisting illnesses were recorded using the conditions in the Charlson index [25]. Menopausal status was determined using the medical oncologists' notes in the medical oncology record, which generally contained enough information to make a determination.

For patients treated in Rochester, the medical record was used to identify whether or not patients had private insurance. For the Henry Ford Health System patients, information on insurance was collected from the Patient Master Index database, a central repository for data on patient encounters at Henry Ford Hospital and all HFHS satellites. Those with Medicare were identified as having private insurance if they indicated having a supplemental policy in addition to Medicare Part A.

For each subject, the address at the time of diagnosis was used to identify the census block group. The socioeconomic information for the census block group, including measures of income and education, was determined from 1990 census data using Landview®III Environmental Mapping Software (US Department of Commerce, Economics and Statistics Administration, Bureau of the Census, 1997). The use of census block group assignment in the assessment of missing individual level SES data has been shown to generate data that correlates with individual level data [26].

The *actual* doses of chemotherapy subjects received were summed across all visits to determine the total dose of each drug. The *expected* doses of chemotherapy were determined using height, weight at the time of the first treatment, and calculated body surface area according to standard chemotherapy protocols. The actual and expected durations of chemotherapy were also determined for each subject.

Outcome measures. We measured four characteristics of chemotherapy treatment. Each measure was calculated for each subject.

(1) Dose proportion: ratio of actual to expected doses of chemotherapy in standard adjuvant chemotherapy regimens. This was calculated for each drug in the chemotherapy regimen. The ratios were then averaged to determine an overall dose proportion for the regimen.
(2) Time ratio: ratio of the actual to expected duration of chemotherapy.
(3) Relative dose intensity (RDI): dose proportion $\times$ 1/time ratio.
(4) Reductions of doses at the initiation of treatment: a measure of whether or not a reduction in the doses of chemotherapy drugs used at the initiation of treatment was documented in the treating provider's note in the subject's chart.

Statistical analyses. Descriptive analyses of the subject characteristics and the outcome measures were performed for the entire sample and by racial/ethnic group. Comparisons between groups were performed using Student's *t*-tests, chi-squared tests, and Fisher's exact tests as appropriate. All tests for significance were two-sided. Dose proportion, the time component, and RDI were analyzed using multivariate regression to determine the effect of race controlling for other subject characteristics, including the body mass index (BMI) categories of the National Heart, Lung, and Blood Institute [27] and initial white blood cell count, tumor characteristics, chemotherapy regimen, treatment site, year of treatment, and reasons for dose changes or treatment delays as independent variables. We included a full set of year of diagnosis indicator variables to account for time effects. We tested down to a specification that included a single indicator variable to identify if treatment occurred after 1993. The multivariate analyses for dose proportion and RDI were performed with cyclophosphamide alone as well as for the other drug(s) in the regimen without the cyclophosphamide. This was done in an attempt to reduce the variability that would arise from rounding doses of oral cyclophosphamide.

Due to the degree of multicollinearity on the SES variables, the dichotomous variable for per capita income above the sample median was the only census block group level SES measure kept in the models. The results were robust to a variety of specifications for the SES variables. Interactions between race and the other covariates were also examined.

As the outcome measures were sufficiently skewed as to result in heteroskedastic error terms, we explored simple transformations for the measures that would normalize the error terms, such as the natural log of the measure. Complex transformations, which would reduce the interpretability of our results, would be required to normalize the error terms. Hence, we opted to use robust standard errors to account for the heteroskedasticity in the error term rather than transform the dependent variables [28]. This generates unbiased parameter estimates but is a less efficient analytical method, resulting in wider confidence intervals than transforming the dependent variables.

Dose reductions at the initiation of treatment were modeled using logistic regression controlling for subject characteristics, including race, age, BMI categories, and initial white blood cell count, tumor characteristics, chemotherapy regimen, treatment site, and year of treatment, parameterized as described above.

Analyses were performed using SAS Version 8.01 (SAS Institute, Inc., Cary, NC) and Stata 7.0 (Stata Corporation, College Station, TX).

Results

Subject characteristics. The African-Americans included in our study were similar to the whites with respect to age, menopausal status, tumor size and number of positive nodes (Tables 1 and 2). African-Americans, however, were more likely to be obese (BMI $\geq$ 30, 43% vs. 21%, $p < 0.0001$) and to live in census block groups with lower per capita income ($12,304 vs. $17,700, $p < 0.0001$). African-Americans were less likely to be privately insured (84% vs. 94%, $p < 0.01$) and were less likely to have ER positive tumors (46% vs. 66%, $p < 0.001$). In addition, African-American women were more likely than white women to have coexisting illnesses. For example, 19% of the African-Americans in our sample had a Charlson index of 1 compared to 8% of the

Table 1. Subject characteristics by race, $n = 489$

	Whites $n = 380$	African-Americans $n = 109$	p-value
Mean age (SD)	48.5 (10.2)	48.6 (10.9)	NS
Menopausal status, n (%)			
Premenopausal	217 (58)	54 (50)	NS
Perimenopausal	25 (7)	8 (7)	
Postmenopausal	134 (36)	46 (43)	
Unknown	4 (0.01)	1 (1)	
Charlson index, n (%)			
0	337 (89)	85 (78)	0.02
1	32 (8)	21 (19)	
2	8 (2)	2 (2)	
3+	3 (1)	1 (1)	
BMI categories, Ref. [27]			
Mean (SD)	26.8 (5.9)	29.5 (7.0)	<0.001
Underweight (BMI $\leq$ 18.5), n (%)	9 (2.3)	3 (2.8)	
Healthy weight (18.5 < BMI < 25), n (%)	156 (41)	29 (26)	
Overweight (25 $\leq$ BMI < 30), n (%)	134 (36)	31 (29)	
Obese (BMI $\geq$ 30), n (%)	81 (21)	46 (43)	
Mean first WBC (SD)	7.1 (2.0)	6.3 (1.9)	<0.001
Use of granulocyte colony stimulating factor, n (%)	22 (5.8)	6 (5.5)	NS
Census block group below poverty level, n (%)	27 (7)	24 (22)	<0.001
Per capita income (SD)	17700 (7000)	12300 (5900)	<0.001
Average median income (SD)	41870 (16789)	26519 (14600)	<0.001
Private insurance, n (%)	357 (94)	92 (84)	0.01
Underinsured, n (%)	24 (6)	17 (16)	<0.001
Dose proportion (mean)	0.85	0.80	0.03
Dose intensity (mean)	0.80	0.76	0.01

whites ($p = 0.001$). There were no differences in the proportion of subjects with higher Charlson scores (2 or more).

Dose proportion and RDI. The mean unadjusted dose proportion among African-Americans was 0.80 compared with a mean unadjusted dose proportion of 0.85 among the whites (difference in dose proportion of 0.05, $p = 0.03$). The mean unadjusted RDI was likewise lower for African-Americans than for whites (0.76 vs. 0.80, $p = 0.01$). There was no difference in the time component between the two groups (1.07 for African-Americans and 1.06 for whites, $p = 0.87$). Seventy-two percent of the whites received a dose proportion of 0.80 or greater compared with only 61% of the African-Americans ($p = 0.02$).

Multivariate regression results. We performed multivariate analyses controlling for tumor characteristics, coexisting medical problems, obesity, per capita income of the subjects' census block group, insurance type (private v.s. non-private), chemotherapy regimen, treatment site, whether chemotherapy was given before or after 1993, and reasons for dose changes and treatment delays (Table 3). The reasons for dose changes and delays are listed in Table 4. Fifteen subjects had missing data, such as tumor size and lymph node status, and were excluded from the multivariate analyses.

Dose proportion. The dose proportion in non-overweight African-Americans was 0.09 lower than in non-overweight whites ($p = 0.002$). Similarly,

Table 2. Tumor characteristics by race, $n = 489$

	Whites ($n = 380$)	African-Americans ($n = 109$)	p-value
Tumor size, n (%)			
<2 cm	173 (46)	39 (36)	0.05
2–5 cm	177 (47)	54 (50)	
>5 cm	30 (8)	16 (15)	
Lymph node involvement, n (%)			
None	136 (36)	41 (38)	0.12
1–3	147 (39)	52 (48)	
4–9	54 (14)	8 (7)	
10+	40 (10)	8 (7)	
Estrogen receptor, n (%)			
Positive	252 (66)	50 (46)	0.001
Negative	122 (32)	58 (53)	
Unknown	6 (2)	1 (1)	
Progesterone receptor, n (%)			
Positive	228 (60)	50 (46)	0.05
Negative	139 (37)	56 (51)	
Unknown	13 (3)	3 (3)	

overweight and obese women, regardless of race, received substantially lower dose proportions than did non-overweight whites (−0.11 in overweight African-Americans, $p < 0.001$; −0.08 in obese African-Americans, $p < 0.01$; −0.02 in overweight whites, $p = 0.14$; −0.09 in obese whites, $p < 0.001$). Initial (pre-treatment) white blood cell count was related to dose proportion in that each rise of $1000\,\mu l^{-1}$ in the white blood cell count was associated with an increase in dose proportion of 0.007. Women with the largest tumors (over 5 cm) received higher dose proportion, which was marginally significant. There were also significant variations in dose proportion by chemotherapy regimen (Table 3). Women treated before 1993 received significantly lower dose proportion. Dose changes due to low ANC, delays or termination of treatment due to side effects, and patients' deciding to terminate chemotherapy were significantly associated with lower dose proportion. Other tumor characteristics, coexisting medical problems, age at diagnosis, insurance status, per capita income and changing regimens were not associated with dose proportion. There were no significant changes in the findings when the dose proportion of cyclophosphamide alone was the dependent variable or when cyclophosphamide was excluded from the analyses.

Time ratio (Table 3). The ratio of the actual to expected time to completion of chemotherapy did not differ between African-Americans and non-overweight whites. The time ratio was, however, 0.04 *lower* in overweight and obese whites than in non-overweight whites. Initial white blood cell count was negatively associated with the time ratio. Changing chemotherapy regimens was associated with a higher time ratio, indicating that changing regimens increased the amount of time it takes women to complete their chemotherapy. In addition, delays in treatment due to low ANC, low white blood cell counts, and missed appointments lengthened the time it took women to complete chemotherapy. There were also significant variations in the time ratio by site and chemotherapy regimen. Age at diagnosis, coexisting medical problems, tumor characteristics, insurance status and per capita income were not significantly related to the time ratio.

Relative dose intensity (Table 3). The RDI in non-overweight African-Americans was 0.10 lower than in non-overweight whites ($p < 0.001$). Overweight and obese African-Americans and obese whites also had significantly lower RDI than non-overweight whites (−0.10 for overweight African-Americans, $p < 0.01$; −0.07 for obese African-Americans, $p < 0.03$, and −0.06 for obese whites, $p < 0.01$). Initial (pre-treatment) white blood cell count was associated with an increase in RDI of 0.012 for each $1000\,\mu l^{-1}$ increase in white blood cell count. Dose changes due to low ANC, delays in treatment due to low white blood cell counts, delays due to missed appointments, and delays or termination of treatment due to side effects were significantly associated with lower RDI, as were patients' deciding to terminate chemotherapy. There were also significant variations by chemotherapy regimen. Increasing age at diagnosis was associated with small but statistically significant decreases in RDI. Women with private insurance received lower RDI. Changing regimens and being treated before 1993 were associated with lower RDI. Women with the largest tumors, those over 5 cm, received higher RDI. Other tumor characteristics, coexisting medical problems, and per capita income were not associated with RDI. There were no significant changes in the findings when the RDI of cyclophosphamide alone was the dependent variable or when cyclophosphamide was excluded from the analyses.

Table 3. Multivariate regression on dose proportion, time ratio and dose intensity, selected results

Variable	Dose proportion		Time ratio		RDI	
	Coefficient (SE)	p	Coefficient (SE)	p	Coefficient (SE)	p
Healthy weight and underweight African-American	−0.089 (0.029)	**0.002**	0.010 (0.016)	0.52	−0.101 (0.030)	**0.001**
Overweight African-American	−0.113 (0.032)	**0.001**	−0.027 (0.021)	0.21	−0.098 (0.032)	**0.003**
Obese African-American	−0.076 (0.029)	**0.009**	−0.025 (0.021)	0.23	−0.066 (0.026)	**0.012**
Overweight white	−0.024 (0.016)	0.14	−0.037 (0.013)	**0.006**	0.003 (0.017)	0.86
Obese white	−0.085 (0.022)	**<0.001**	−0.036 (0.015)	**0.02**	−0.058 (0.022)	**0.009**
Age at diagnosis	−0.001 (0.0007)	0.12	0.0002 (0.0006)	0.74	−0.002 (0.0007)	**0.03**
Comorbid conditions (Charlson index ≥ 1)	0.021 (0.020)	0.29	−0.002 (0.017)	0.89	0.026 (0.021)	0.21
No lymph node involvement	−0.026 (0.016)	0.11	−0.012 (0.013)	0.33	−0.022 (0.016)	0.18
Private insurance	−0.040 (0.027)	0.14	0.008 (0.021)	0.71	−0.053 (0.027)	**0.05**
Census block group per capita income > median	0.011 (0.015)	0.48	0.010 (0.012)	0.41	0.003 (0.016)	0.85
Dose changes due to low ANC	−0.035 (0.014)	**0.01**	–	–	−0.026 (0.012)	**0.03**
Delays due to low ANC	0.023 (0.008)	**0.004**	0.027 (0.007)	**<0.001**	−0.001 (0.007)	0.87
Delays due to low white blood cell counts	−0.001 (0.008)	0.90	0.028 (0.007)	**<0.001**	−0.018 (0.008)	**0.02**
Delays due to missed appointments	−0.008 (0.026)	0.76	0.056 (0.018)	**0.002**	−0.048 (0.024)	**0.04**
Delays and termination of treatment due to side effects	−0.167 (0.036)	**<0.001**	0.008 (0.019)	0.69	−0.172 (0.032)	**<0.001**
Termination of treatment due to patient decision	−0.241 (0.084)	**0.004**	−0.111 (0.046)	**0.02**	−0.169 (0.084)	**0.04**
Treated before 1993	−0.042 (0.016)	**0.008**	−0.017 (0.013)	0.17	−0.035 (0.156)	**0.03**
Compared to CA*						
CAF intravenous, day 1, q. 21 days	−0.173 (0.029)	**<0.001**	0.028 (0.027)	0.30	−0.183 (0.030)	**<0.001**
CAF oral, days 1, 8, q. 28 days	−0.101 (0.027)	**<0.001**	−0.075 (0.020)	**<0.001**	−0.057 (0.029)	**0.05**
CMF intravenous, days 1, 8, q. 21 days	−0.052 (0.020)	**0.008**	0.048 (0.019)	**0.01**	−0.084 (0.023)	**<0.001**
CMF intravenous, day 1, q. 21 days	−0.036 (0.034)	0.29	0.050 (0.033)	0.13	−0.071 (0.035)	**0.04**
CMF intravenous, days 1, 8, q. 28 days	−0.001 (0.047)	0.98	−0.102 (0.050)	**0.04**	0.090 (0.059)	0.13
CMF oral, days 1, 8, q. 28 days	−0.087 (0.019)	**<0.001**	−0.047 (0.019)	**0.012**	−0.057 (0.022)	**0.01**
CNF	−0.088 (0.034)	**0.010**	−0.052 (0.031)	0.09	−0.116 (0.036)	**0.001**
Change in regimen	−0.029 (0.029)	0.31	0.127 (0.019)	**<0.001**	−0.057 (0.024)	**0.02**

* C = cyclophosphamide, A = doxorubicin (adriamycin), M = methotrexate, F = 5-fluorouracil, N = mitoxantrone.

First cycle dose reductions. Logistic regressions on dose reductions at the initiation of treatment generated findings similar to the patterns described above (Table 5). Non-overweight African-Americans (OR = 3.7, $p < 0.05$), overweight African-Americans (OR = 19.4, $p < 0.001$), obese African-Americans (OR = 11.5, $p < 0.001$), overweight whites (OR = 5.2, $p < 0.001$), and obese whites (OR = 21.4, $p < 0.001$) were more likely to have first cycle dose reductions than were non-overweight whites. Initial dose reductions were more common before 1993 (OR = 3.5, $p < 0.001$). Women living in census block groups with per capita incomes above the median for our sample were less likely to have their first cycle doses reduced. There were significant differences by treatment site in the tendency to reduce doses at the start of treatment. Tumor characteristics, chemotherapy regimen, co-existing medical problems, age at diagnosis, white blood cell count at the start of treatment, and insurance status were not associated with initial cycle dose reductions.

Table 4. Frequency of dose changes and delays in treatment by race

Variable	Whites	African-Americans	*p*-value
Dose changes and number of dose changes, *n* (%)			
Dose changes due to low ANC, *n* (%)	75 (19.7)	17 (15.6)	NS
Mean number for those having dose changes	1.4	2.2	NS
Dose changes due to low white blood cell counts, *n* (%)	64 (16.8)	18 (16.5)	NS
Mean number for those having dose changes	1.5	1.8	NS
Dose changes due to side effects, *n* (%)	56 (14.7)	12 (11.0)	NS
Mean number for those having dose changes	1.3	1.2	NS
Dose changes due to weight loss, *n* (%)	10 (2.6)	5 (4.6)	NS
Mean number for those having dose changes	1.5	1.0	NS
Delays and number of delays			
Delays due to acute illness, *n* (%)	17 (4.7)	12 (11.0)	**0.01**
Mean number for those having delays	1.0	1.3	0.10
Delays due to hospitalization, *n* (%)	26 (6.8)	1 (0.9)	**0.02**
Mean number for those having delays	1.2	1.0	NS
Delays due to low ANC, *n* (%)	155 (40.8)	27 (24.8)	**0.002**
Mean number for those having delays	1.6	2.0	NS
Delays due to low white blood cell counts, *n* (%)	114 (30.0)	28 (25.7)	NS
Mean number for those having delays	1.7	2.0	NS
Delays due to missed appointments, *n* (%)	3.2 (12)	8.3 (9)	**0.02**
Mean number for those having delays	1.1	1.8	0.07
Delays and termination of treatment due to side effects, *n* (%)	30 (7.9)	7 (6.4)	NS
Mean number for those having delays	1.1	1.1	NS
Delays due to surgical complications, *n* (%)	2 (0.5)	2 (1.8)	NS
Mean number for those having delays	1	1.5	NS
Delays due to vacations, *n* (%)	11 (2.9)	2 (1.8)	NS
Mean number for those having delays	1.1	1.0	NS
Termination of treatment due to patient decision, *n* (%)	4 (1.1)	4 (3.7)	0.06

Table 5. Logistic regression to predict dose reductions at initiation of treatment, selected results

Variable	Odds ratio	95% CI	*p*
Healthy weight and underweight white	1.00	–	–
Healthy weight and underweight African-American	3.73	1.27–10.96	**0.02**
Overweight African-American	19.39	4.57–82.21	**<0.001**
Obese African American	11.54	3.21–41.54	**<0.001**
Overweight white	5.19	2.19–12.29	**<0.001**
Obese white	21.40	7.88–58.10	**<0.001**
Age at diagnosis	1.02	0.99–1.05	0.18
Presence of comorbidity	0.50	0.18–1.36	0.17
White blood cell count at start of chemotherapy	1.02	0.86–1.21	0.81
Private insurance	1.55	0.56–4.28	0.40
Census block group per capita income > median	0.49	0.25–0.98	**0.04**
Treated before 1993	3.48	1.63–7.41	**0.001**

Discussion

We have identified systematic differences in the administration of chemotherapy given to African-American women and to overweight and obese women regardless of race. African-Americans and overweight and obese women in our sample received lower adjuvant chemotherapy dose proportion and dose intensity after correcting for clinical and other sociodemographic characteristics. We have also demonstrated that more African-Americans had chemotherapy dose reductions for the first cycle of treatment, independent of weight and that overweight and obese women had more initial dose reductions, independent of race. The relationships between race and BMI and our outcome measures of dose proportion, dose intensity, and first cycle dose reductions were strengthened when we controlled for tumor characteristics, coexisting medical problems, income, type of insurance, and reasons for dose changes and treatment delays (including missed appointments).

Biological and medical reasons, such as differences in tolerance of therapy, comorbidity, or leukocyte counts, do not explain the differences in adjuvant chemotherapy treatment between African-American and white women. There is no evidence in our subjects that the African-American patients experienced more chemotherapy dose delays due to side effects than whites, and in fact others have found that there may be greater tolerance of therapy among African-Americans [29]. We also found no evidence that delays due to low ANC account for the lower dose proportion and RDI among African-Americans; more of the whites in our sample had delays in treatment due to low ANC (40.8% of whites v.s. 24.8% of African-Americans, $p = 0.002$). Thus, despite the association of black race with lower leukocyte counts [30, 31], we found no evidence that lower white blood cell counts accounted for the difference in dose proportion or RDI among the whites and African-Americans in our sample.

Measures of SES, such as per capita income of the census block group and the type of health care insurance, do not appear to play a role in the treatment differences we found. It is likely that SES would play a greater role in patterns of care such as referral for chemotherapy, recommendations for chemotherapy, and perhaps acceptance of therapy by the patient rather than the quality of chemotherapy administered once the decision to treat with adjuvant chemotherapy is made. Missed appointments, more common in the African-Americans, were associated with a lower dose intensity and may reflect the challenges posed by economic obstacles, such as difficulties with transportation or with job-related barriers. A limitation of this study is the fact that income and education information were not available at the level of the individual. Most of our measures of SES (other than type of insurance) are based on census block group assignment. The use of census-level data has been validated as a method for overcoming missing socioeconomic data in patient records [26], but had we been able to collect individual-level SES information, such as income, education, wealth, and occupation, we may have found an association with SES and our measures of quality of care. Moreover, chart audit, no matter how detailed, cannot provide information on family roles, such as care of young children or elderly parents, and social support networks. These factors may account for some of the observed treatment differences between ethnic groups.

Much of the literature on health care disparities has demonstrated that African-Americans are less likely than whites to receive intervention for the same condition. For example, Bach et al. demonstrated that African-Americans are less likely to have potentially curative surgery for stage I or II lung cancer [32], and Mandelblatt et al. recently confirmed previous findings that African-American Medicare beneficiaries are less likely to have radiation therapy after breast conserving surgery [33]. In these cases, it is difficult to determine at which point in the process of care the disparity arises: Are patients not being referred for surgery or radiation? Are they not being offered such therapies? Or are they declining treatments that are offered to them? Our study focuses on the patterns of care in patients who have been referred to medical oncology care, have been advised to receive chemotherapy, and have agreed to start adjuvant chemotherapy. Our process measures of dose proportion and RDI are focused therefore on what has been called 'realized access', that is, access to and receipt of high quality care necessary for favorable outcomes [34]. It appears that African-American women are experiencing a different process of care than the white women and that two of the possible factors – biological and socioeconomic factors – do not explain these variations.

An additional explanation for the racial disparities in the administration of chemotherapy we describe is that interactions between health care providers and their African-American patients differ from those with

their white patients [35–38]. Health care providers, the majority of whom are non-minority, may hold beliefs and assumptions, conscious or unconscious, about their patients' ability to comply with or to tolerate chemotherapy and the side effects, and these assumptions may differ according to patient race/ethnicity. In a survey of 193 physicians with a total of over 618 patient encounters, physicians perceived African-American patients as, among other things, less likely to adhere to medical advice, more likely to lack social support, and less likely to participate in cardiac rehabilitation [37]. In our study, the association between race and first cycle dose reductions may reflect similar differences in physician assumptions about their African-American patients in terms of the patients' social support or ability to tolerate chemotherapy. The disparities in care that we have described may also reflect communication gaps between patient and provider about, for example, the goals of therapy, the anticipated side effects, the management of side effects, and the potential impact of dose reductions and delays [35, 37, 39].

As with African-American women, overweight and obese women appear to be experiencing systematic differences in chemotherapy administration independent of comorbidity, SES, treatment site, and age. Multiple investigators have challenged the practice of reducing chemotherapy doses in obese women, a practice motivated by a desire to avoid excessive toxicity. There is mounting evidence that obese women do not experience increased toxicity when dosed according to actual body weight and that the use of ideal or adjusted body weight may in fact compromise efficacy [21, 22, 40, 41].

Of note, our findings did not apply only to the obese women (BMI ≥ 30). Compared to healthy weight and underweight whites, whites who are classified as 'overweight' ($25 \leq$ BMI < 30) were over five times as likely to have a first cycle dose reduction, and overweight African-Americans were 19 times more likely to experience such a dose reduction. Our results are similar to those in a study of over 500 women treated with breast cancer adjuvant chemotherapy between 1990 and 1998 at a single site in Toronto, Ontario. In this study, the majority of patients prescribed a first cycle dose reduction were overweight rather than obese [20]. Our finding that dose reductions for the first cycle of chemotherapy were less common after the 1993 suggests that some providers have changed their prescribing practices for some of their patients.

We studied women treated before the widespread use of granulocyte colony stimulating factor (G-CSF) in patients undergoing breast cancer adjuvant chemotherapy. Practice patterns and the resulting dose proportion and dose intensity may be altered by use of G-CSF; the impact of G-CSF on dose proportion and dose intensity in different populations would be an area worth investigating.

Further exploration of the underlying reasons for these discrepancies in the administration of adjuvant chemotherapy may identify correctable causes of outcome disparity in breast cancer. Dose proportion and dose intensity of standard dose adjuvant chemotherapy, measured using the RDI or the summation dose intensity of Hryniuk et al.[42], may represent measures of quality of care [43] that could be used further in examining disparities in cancer outcome. In particular, the practice of first cycle dose reduction that we observed suggests differences in prescribing patterns according to patient characteristics.

Would our findings be replicated in other populations in, for example, other geographic locations and other practices? If so, the strength of the associations between race and BMI with dose proportion and intensity would be compelling. If our findings were not consistently seen in other settings, such variability in practice would further suggest that dose proportion, dose intensity, and the use of first cycle dose reductions are all modifiable patterns of care.

Acknowledgements

The authors wish to acknowledge Frances A. Collichio, MD for her contribution to the initial concept for the project. This work has been supported by the US Army Medical Research and Materiel Command under DAMD17-00-1-0422 and by the Doris Duke Charitable Foundation.

References

1. SEER website. See http://www.census.gov. SEER website 2003
2. Newman LA, Mason J, Cote D, Vin Y, Carolin K, Bouwman D, Colditz GA: African-American ethnicity, socioeconomic status, and breast cancer survival: A meta-analysis of 14 studies involving over 10,000 African-American and 40,000 White American patients with carcinoma of the breast. Cancer 94: 2844–2854, 2002
3. Eley JW, Hill HA, Chen VW, Austin DF, Wesley MN, Muss HB, Greenberg RS, Coates RJ, Correa P, Redmond CK, et al.:

Racial differences in survival from breast cancer. Results of the National Cancer Institute Black/White Cancer Survival Study. JAMA 272: 947–954, 1994
4. Joslyn SA, West MM: Racial differences in breast carcinoma survival. Cancer 88: 114–123, 2000
5. Bradley CJ, Given CW, Roberts C: Race, socioeconomic status, and breast cancer treatment and survival. J Natl Cancer Inst 94: 490–496, 2002
6. Yood MU, Johnson CC, Blount A, Abrams J, Wolman E, McCarthy BD, Raju U, Nathanson DS, Worsham M, Wolman SR: Race and differences in breast cancer survival in a managed care population. J Natl Cancer Inst 91: 1487–1491, 1999
7. Perkins P, Cooksley CD, Cox JD: Breast cancer. Is ethnicity an independent prognostic factor for survival? Cancer 78: 1241–1247, 1996
8. Bassett MT, Krieger N: Social class and black-white differences in breast cancer survival. Am J Public Health 76: 1400–1403, 1986
9. Cross CK, Harris J, Recht A: Race, socioeconomic status, and breast carcinoma in the US: What have we learned from clinical studies. Cancer 95: 1988–99, 2002
10. Shavers VL, Harlan LC, Stevens JL: Racial/ethnic variation in clinical presentation, treatment, and survival among breast cancer patients under age 35. Cancer 97: 134–147, 2003
11. Roach III M, Cirrincione C, Budman D, Hayes D, Berry D, Younger J, Hart R, Henderson IC: Race and survival from breast cancer: Based on Cancer and Leukemia Group B trial 8541. Cancer J Sci Am 3: 107–112, 1997
12. Dignam JJ: Efficacy of systemic adjuvant therapy for breast cancer in African-American and Caucasian women. J Natl Cancer Inst Monogr 36–43, 2001
13. Bonadonna G, Valagussa P: Dose–response effect of adjuvant chemotherapy in breast cancer. New Engl J Med 304: 10–15, 1981
14. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C: Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. New Engl J Med 332: 901–906, 1995
15. Wood WC, Budman DR, Korzun AH, Cooper MR, Younger J, Hart RD, Moore A, Ellerton JA, Norton L, Ferree CR, et al.: Dose and dose intensity of adjuvant chemotherapy for Stage II, node-positive breast carcinoma. New Engl J Med 330: 1253–1259, 1994
16. Budman DR, Berry DA, Cirrincione CT, Henderson IC, Wood WC, Weiss RB, Ferree CR, Muss HB, Green MR, Norton L, Frei E3: Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. J Natl Cancer Inst 90: 1205–1211, 1998
17. Colleoni M, Price K, Castiglione-Gertsch M, Goldhirsch A, Coates A, Lindtner J, Collins J, Gelber RD, Thurlimann B, Rudenstam CM: Dose–response effect of adjuvant cyclophosphamide, methotrexate, 5-fluorouracil (CMF) in node-positive breast cancer. International Breast Cancer Study Group. Eur J Cancer 34: 1693–1700, 1998
18. Muss HB, Hunter CP, Wesley M, Correa P, Chen VW, Greenberg RS, Eley JW, Austin DF, Kurman R, Edwards BK: Treatment plans for black and white women with Stage II node-positive breast cancer. The National Cancer Institute Black/White Cancer Survival Study experience. Cancer 70: 2460–2467, 1992
19. Kiefe CI: Race/ethnicity and cancer survival: the elusive target of biological differences. JAMA 287: 2138–2139, 2002
20. Madarnas Y, Sawka CA, Franssen E, Bjarnason GA: Are medical oncologists biased in their treatment of the large woman with breast cancer? Breast Cancer Res Treat 66: 123–133, 2001
21. Rosner GL, Hargis JB, Hollis DR, Budman DR, Weiss RB, Henderson IC, Schilsky RL: Relationship between toxicity and obesity in women receiving adjuvant chemotherapy for breast cancer: results from Cancer and Leukemia Group B Study 8541. J Clin Oncol 14: 3000–3008, 1996
22. Smith TJ, Desch CE: Neutropenia-wise and pound-foolish: Safe and effective chemotherapy in massively obese patients. South Med J 84: 883–885, 1991
23. Flegal KM, Carroll MD, Ogden CL, Johnson CJ: Prevalence and trends in obesity among US adults, 1999–2000. JAMA 288: 1723–1727, 2002
24. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS: Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 289: 76–79, 2003
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40: 373–383, 1987
26. Krieger N: Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. Am J Public Health 82: 703–710, 1992
27. nhlbisupport.com/bmi 2003
28. Greene WH: Econometric Analysis. 2nd edn, 1993
29. McCollum AD, Catalano PJ, Haller DG, Mayer RJ, MacDonald JS, Benson AB3, Fuchs CS: Outcomes and toxicity in African-American and Caucasian patients in a randomized adjuvant chemotherapy trial for colon cancer. J Natl Cancer Inst 94: 1160–1167, 2002
30. Reed WW, Diehl LF: Leukopenia, neutropenia, and reduced hemoglobin levels in healthy American blacks. Arch Int Med 151: 501–505, 1991
31. Castro OL, Haddy TB, Rana SR: Age- and sex-related blood cell values in healthy black Americans. Public Health Rep 102: 232–237, 1987
32. Bach PB, Cramer LD, Warren JL, Begg CB: Racial differences in the treatment of early-stage lung cancer. N Engl J Med 341: 1198–1205, 1999
33. Mandelblatt JS, Kerner JF, Hadley J, Hwang YT, Eggert L, Johnson LE, Gold K: Variations in breast carcinoma treatment in older Medicare beneficiaries: Is it black or white? Cancer 95: 1401–1414, 2002
34. Mandelblatt JS, Yabroff KR, Kerner JF: Equitable access to cancer services: a review of barriers to quality care. Cancer 86: 2378–2390, 1999
35. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. 2002
36. van Ryn M: Research on the provider contribution to race/ethnicity disparities in medical care. Med Care 40: I140–I151, 2002
37. van Ryn M, Burke J: The effect of patient race and socioeconomic status on physicians' perceptions of patients. Soc Sci Med 50: 813–828, 2000
38. Cooper-Patrick L, Gallo JJ, Gonzales JJ, Vu HT, Powe NR, Nelson C, Ford DE: Race, gender, and partnership in the patient-physician relationship. JAMA 282: 583–589, 1999
39. Balsa AI, McGuire TG: Statistical discrimination in health care. J Health Econ 20: 881–907, 2001
40. Poikonen P, Blomqvist C, Joensuu H: Effect of obesity on the leukocyte nadir in women treated with adjuvant

cyclophosphamide, methotrexate, and fluorouracil dosed according to body surface area. Acta Oncol 40: 67–71, 2001

41. Gelman RS, Tormey DC, Betensky R, Mansour EG, Falkson HC, Falkson G, Creech RH, Haller DG: Actual versus ideal weight in the calculation of surface area: effects on dose of 11 chemotherapy agents. Cancer Treat Rep 71: 907–911, 1987
42. Hryniuk W, Frei III E, Wright FA: A single scale for comparing dose-intensity of all chemotherapy regimens in breast cancer: summation dose-intensity. J Clin Oncol 16: 3137–3147, 1998
43. Morrow T, Siegel M, Boone S, Lawless G, Carter W: Chemotherapy dose intensity determination as a quality of care measure for managed care organizations in the treatment of early-stage breast cancer. Am J Med Qual 17: 218–224, 2002

Address for offprints and correspondence: Jennifer J. Griggs, MD, MPH, Department of Medicine, Hematology/Oncology and Department of Community and Preventive Medicine, University of Rochester, 601 Elmwood Avenue, Box 704, Rochester, NY 14642, USA; *Tel.:* +1-585-275-4797; *Fax:* +1-585-756-4448; *E-mail:* jennifer_griggs@urmc.rochester.edu